REMARKS

A check for the fee for a one month extension of time accompanies this response. Any additional fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is required, this paper is to be considered such Petition.

The Examiner is thanked for her courtesy in granting an interview to clarify the Office Action and to discuss proposed amendments. Claim 4 is amended as discussed in the telephonic interview.

As suggested by the Examiner, an executed DECLARATION under 37 C.F.R. §1.132 of Köster, is attached hereto.

Claims 4 and 11-16 are pending. Claim 4 is amended. The amendment finds basis in original claims 1, 3 and 4.

THE REJECTION OF CLAIMS 4 and 11-16 UNDER 35 U.S.C. §112, FIRST PARAGRAPH: NEW MATTER REJECTION

Claims 4 and 11-16 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors(s), at the time the application was filed, had possession of the claimed invention. The Office Action contends that the expression "each molecule (nucleotide or nucleoside) contains 3 to 10 reactive moieties" in claims 4 and 11-16 has no clear support in the specification and the claims as originally filed. The Office Action urges that the specification discloses the use of 3 or more reactive groups that are protected by 3 or more different protecting groups on more than one nucleotide. The office Action alleges that the subject matter claimed in claims 4 and 11-16 broadens the scope of the invention as originally disclosed in the specification. The rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of

filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

Analysis

Claim 4, as amended herein recites:

> A process for generating a combinatorial library, comprising the steps of:
> (a) preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 reactive moieties, each reactive moiety being blocked by a blocking group, wherein the three blocking groups on each immobilized molecule are independently removable under three different conditions; and
> (b) removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library.

The claim finds basis in original claims 1, 3 and 4. Original claim 1 recites:

> A process for generating a combinatorial set of molecules of core structure M, comprising the steps of:
> (a) preparing a plurality of immobilized molecules of core structure M, wherein said molecules contain a plurality of reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups are independently removable under at least three different conditions, and
> (b) removing certain blocking groups and derivatizing the resulting reactive moieties in a preprogrammed, regioselective manner, wherein each member of a combinatorial set is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial set of molecules of core structure M.

Claim 3 further defines that the immobilized molecule is a multifunctional, low molecular weight compound that has **3 to 10** deprotectable moieties. Claim 4 describes the low molecular weight compound as being selected from

nucleoside and nucleotide among other things. Thus, the recitation "each molecule(nucleotide or nucleoside) contains 3 reactive moieties" claimed in the instant claims has a clear basis in the application as originally filed.

Therefore, the subject matter claimed in claims 4 and 11-16 does not broaden the scope of the disclosure as originally filed.

REJECTION OF CLAIMS 4 AND 11-16 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION

Claims 4 and 11-16 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is alleged that the instant claims are directed to generating a combinatorial library in which there is no claimed structure or other identifying characteristics presented with respect to the final combinatorial compounds and types of blocking groups used such that they are removable under at least three different conditions. It is further alleged that the specification description is directed to synthesis of oligonucleotide synthesis using modified nucleobases with multiple protecting groups attached. It is urged that this description does not provide an adequate representation of the instantly claimed method. The Office Action urges that no identifying characteristics regarding the combinatorial library of compounds prepared using the claimed method are described. It is further alleged that the specification does not disclose the use of an immobilized single nucleotide with 3 reactive moieties which are removed by 3 different conditions. The Office Action urges that the narrow scope of examples directed to the use of specific protection groups and reaction conditions present on an oligomer are not representative of the scope of the presently claimed method. Applicant respectfully traverses this rejection.

RELEVANT LAW

As discussed above.

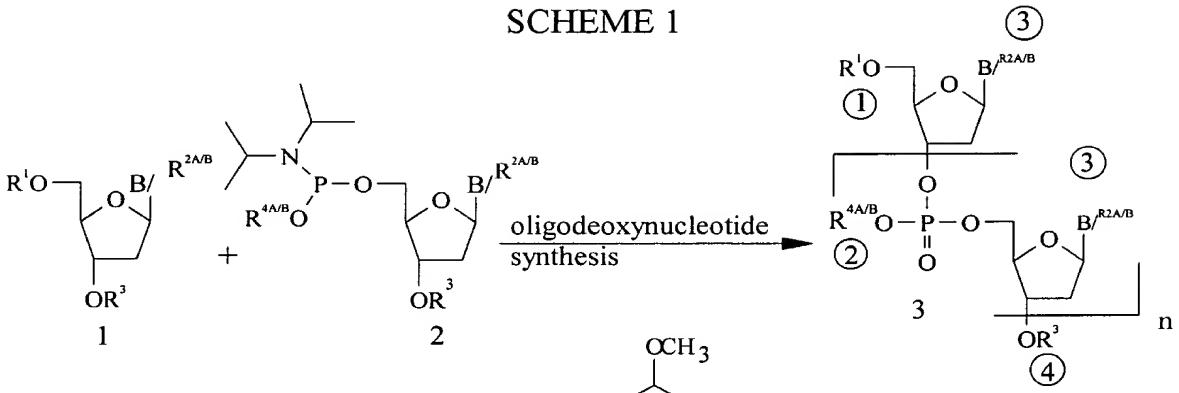
Instant claims 4 and 11-16

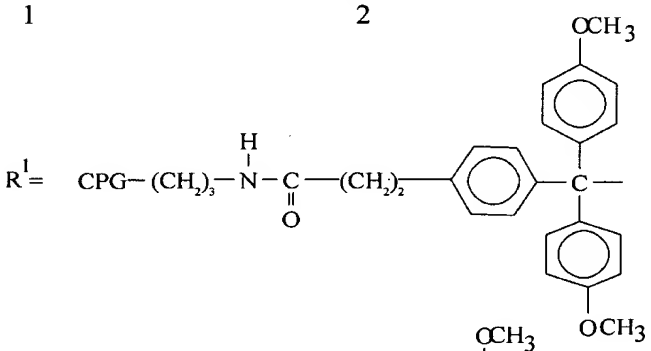
Claim 4 is discussed above. Claims 11-16 depend from claim 4 and further define the process of claim 4.

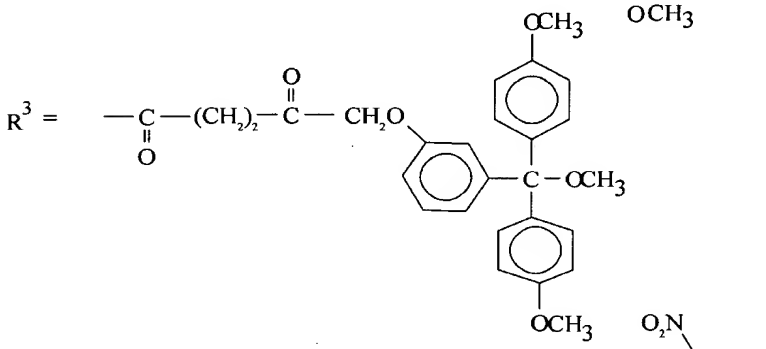
ANALYSIS

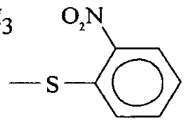
Applicant respectfully submits that the specification on page 7 discloses general structures for exemplary molecules selected from a nucleoside and a nucleotide, wherein each molecule contains 3 reactive moieties AND each moiety is blocked by a different blocking group which are independently removable under three different conditions as follows:

SCHEME 1







nps = 2-nitrophenylsulfenyl : 

$B/^{R^{2A/B}}$ = B or $B^{R^{2A}}$ or $B^{R^{2B}}$

$R^{4A/B} = R^{4A}$ or R^{4B}

$R^{2A/B} = R^{2A}$ or R^{2B}

R^{4A} = β-cyanoethyl as protecting group for selective and orthogonal deprotection with reagent II (table 1),

R^{4B} = a protecting group stable with reagent II (table 1),
B = a natural or modified base, which does not require a protecting group during synthesis,
B^{R2A}, B^{R2B} = a natural or modified nucleobase with a protecting group,
R^{2A}, R2B = different protecting groups, e.g. R^{2A} is the nps protecting group in: N^4-nps-cytosine (C^{nps}), N^6-npa-adenine (A^{nps}), N^2-nps-guanine (G^{nps}) for selective and orthogonal deprotection according to table 1 and e.g. R^{2B} is the npeoc,npe protection in: N^4-npeoc-cytosine (C^{npeoc}), N^6-npeoc-adenine (A^{npeoc}), N^2-npeoc-O^6-npe-guanine ($G^{npeoc,npe}$) stable under the deprotection conditions of table 1, npeoc = 2-(4-nitrophenyl)-ethoxycarbonyl, npe = 1-(4-nitrophenyl)-ethyl.
n: number of condensation reactions; ①, ②, ③, ④ : protective positions;
CPG: Controlled-Pore-Glass.

Compound 1 shown in scheme 1 represents an immobilized nucleoside with three different reactive groups and compound 2 represents example of a nucleotide with three reactive groups protected with three different blocking groups. A person of skill in the art would recognize that nucleosides/nucleotides containing ribose as a sugar moiety would represent further compounds with three reactive moieties that can be blocked by three different protecting groups as described in the application, for generation of combinatorial libraries as instantly claimed. The application discloses exemplary set of blocking groups and a set of reagents for selective orthogonal deprotection thereof, to generate a combinatorial library of nucleosides/nucleotides as instantly claimed. The application discusses various other blocking groups removable under conditions of selective orthogonal deprotection on pages 13 and 14. Examples 1 and 2 on pages 30-40, exemplify preparation of nucleosides/nucleotides with three different blocking groups removable under three different conditions. Based on the application disclosure above, a skilled artisan would be able to generate a combinatorial library of nucleosides/nucleotides as instantly claimed.

Therefore, the application as originally filed provides adequate disclosure for the instantly claimed process for generating a combinatorial library of nucleosides and nucleotides. The Examiner is reminded that there is no requirement to prepare any or all embodiments of the claimed process to satisfy

written description requirement and examples are not required to satisfy written description. The application as originally filed, discloses the instantly claimed process, the nucleosides/nucleotides with three reactive moieties blocked with three different blocking groups and conditions for removal thereof are disclosed in the application. Further, possession does not mean physical possession but appreciation. In light of the discussion presented above, the application clearly conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the presently claimed subject matter. Specifically, it is clear from the disclosure that the claimed combinatorial library can be generated by choosing appropriate starting materials, blocking groups and reactions conditions for selective orthogoal deprotections as disclosed in the application.

Rebuttal to Examiner's Arguments

Applicant herein provides response to the specific issues raised in the Office action.

1) **Identifying characteristics**

The Office Action alleges that no identifying characteristics regarding the combinatorial library of compounds prepared using the claimed method are described.

Applicant respectfully submits that claim 4 recites "plurality of immobilized molecules selected from **a nucleoside and a nucleotide**". Therefore, instantly claimed process is intended to generate a combinatorial library of nucleosides/nucleotides as described therein. The application provides description of the reactive moieties on nucleosides/nucleotides and discloses that they are blocked by three different blocking groups that can be removed under three different conditions. Further, the application discloses that the reactive moieties can be uniquely derivatized to generate combinatorial library as instantly claimed. Chemical structures of exemplary nucleosides/nucleotides are disclosed in the application and are known to a skilled artisan. Furthermore, it is

not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge.

2) **Use of 3 different protecting groups present on an oligomer**

The Office Action alleges that the specification disclosure is based on the use of 3 different protecting groups present on an oligomer and methods for deprotecting the 3 different protecting groups at different reaction conditions.

As discussed above, the specification on pages 7, 22 and 23, discloses a single nucleoside/nucleotide with 3 different protecting groups, for example, the phosphate protection is achieved by β-cyanoethyl group, 5'-OH group is protected with dimethoxytrityl group and the bases are protected with nps, npeoc and/or npe protecting groups and on page 9, the specification discloses conditions for selective removal of the protecting groups. Therefore, the specification discloses a single nucleotide with three reactive moieties blocked by three different blocking groups.

THE REJECTION OF CLAIMS 4 AND 11-16 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT

Claims 4, 11-16 are rejected by the Office Action under 35 U.S.C. §112, first paragraph, for lack of enablement. It is urged that, specification, while being enabling for the use of specific linkers (npeoc, npc and nps) with specific reactions (deprotection reactions), does not reasonably provide enablement for any type of protecting groups and deprotection reagents. It is further alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. It is alleged in the Office Action that the specification disclosure is based on the use of specific protecting groups and specific reactions and conditions to remove the protecting groups. Applicant respectfully traverses this rejection.

RELEVANT LAW

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use

the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of 35 U.S.C. §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require **undue** experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without **undue** experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude

that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against **the claimed subject matter**. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect to scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

Analysis

As demonstrated below, it would not require undue experimentation to (i) block the reactive moieties on the nucleosides/nucleotides with three different protecting groups (ii) deprotect those groups under three different conditions and (iii) generate a combinatorial library within the scope of the claims, in view of the knowledge and level of skill in the art and the teachings and disclosure in the specification regarding the use of protecting groups and conditions for selective orthogonal deprotection.

The level of knowledge and skill in the nucleoside/nucleotide chemistry, including structures thereof, the reactive moieties present and blocking/deblocking the reactive moieties on nucleosides and nucleotides, was so high as of the effective filing date that it would not have required extensive experimentation by one of skill in the art to select blocking groups other than

the ones demonstrated in the application, removable under three different conditions, based on the description of exemplary blocking groups/deblocking conditions in the application and generate a combinatorial library as claimed in claim 4. Furthermore, the specification describes three exemplary blocking groups and their use in protecting reactive moieties in nucleoside/nucleotide molecules under selective orthogonal deprotection conditions.

Scope of the claims

As discussed above claim 4 is directed to a process for generating a combinatorial library, comprising the steps of preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 reactive moieties, each reactive moiety being blocked by a blocking group, wherein the three blocking groups on each immobilized molecule are independently removable under three different conditions; and removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library. Claims 11-16 depend from claim 4 and further define the process of claim 4.

Thus the claims are directed to a process for generating a combinatorial library which is described in the specification in detail by disclosing all the steps involved. For example, the specification describes the blocking groups and deblocking conditions for reactive moieties on nucleosides/nucleotides on pages 7, 9, 22 and 23. The specification, including the working examples, describe preparation of nucleosides/nucleotides with three different blocking groups. Various blocking groups for the reactive moieties in the molecules, for example, phosphate group, hydroxy group on sugar and nucleoside bases are well characterized in the instant application and are well known to those of skill in the art, as are the deprotecting reagents for selective orthogonal deprotection (see pages 12-13). Furthermore the specification discloses stability of various

protecting groups under the reaction conditions of orthogonal deprotection and cites a large number of articles, to describe protecting groups for reactive moieties on nucleosides/nucleotides. Therefore the claim 4, and claims 11-16 dependent thereon, are directed to a process for generating a combinatorial library which is described in the specification.

The level of skill in the art is high

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art.

Knowledge of those of skill in the art:

At the time of the effective filing date of this application and before, the skilled artisan knew various protecting groups and deprotection reagents and conditions for use in nucleotide/nucleoside synthesis. Further, there is a large body of literature directed to the use and stability of various protecting groups under different reaction conditions. Selective removal of various protecting groups by using deprotection reagents is also well recorded in the art and known to those of skill in the art. As discussed in detail in the attached DECLARATION of Dr. Köster, the articles cited in the specification and of record in this application describe various protecting groups for reactive functionalities in nucleoside/nucleotide synthesis.

The amount of direction and guidance presented, teachings in the specification and presence of working examples

The specification describes blocking of reactive moieties in nucleosides/nucleotides with three different blocking groups, such as β-cyanoethyl group for the phosphate protection, dimethoxytrityl group for the 5'-OH group and nps, npeoc and/or npe protecting groups for the bases, that can be selectively and orthogonally deprotected (Scheme 1, page 7-8). The specification describes and exemplifies various other phosphate and base

protecting groups and their stability during deprotection reactions (see page 13, lines 7-21, pages 14-15, lines 20-10, pages 19-20, lines 13-15, page 24, lines 1-15). Numerous articles cited in the application teach the use of various protecting groups for protection of reactive functionalities in solid phase synthesis of combinatorial libraries and deprotection reagents and conditions. The working examples provided exemplify nucleosides/nucleotides with three different protecting groups, which can be removed under three different conditions for subsequent derivatization to arrive at claimed combinatorial libraries.

Conclusion

In light of the scope of the claims, the teachings in the specification, the high level of skill of those in this art, and the extensive knowledge of those of skill in this art, it would not require undue experimentation for a person of skill in the art to select blocking groups to block reactive moieties wherein 3 blocking groups are removable under 3 different conditions that are within scope of the instant claims, and subsequently derivatize the reactive moieties with unique substituents to generate the claimed combinatorial libraries of nucleotides or nucleosides. As described in the DECLARATION of Dr. Köster, the specification describes and exemplifies nucleosides/nucleotides with three different blocking groups. Further, as discussed in the DECLARATION, one of skill in the art, based on the references cited in the specification, would know how to select other protecting groups within the scope of the instant claims. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. It would be unfair and unduly limiting to require the applicant to limit the claims to the

exemplified blocking groups/deblocking conditions when the specification clearly places those of skill in the art in possession of all the other blocking groups that are known in the field of nucleoside/nucleotide chemistry for protection of reactive moieties in nucleosides/nucleotides to generate a combinatorial library as instantly claimed. Therefore, it would be unfair, unduly limiting and contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims only to the exemplified blocking groups:

See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to limit the claims to only the exemplified blocking groups would permit those of skill in the art to practice what is disclosed in the application, but avoid infringing such limited claims. One of skill in the art could readily choose different blocking groups and modify the reaction conditions for selective orthognal deprotection as taught in the specification. The first paragraph of §112 requires only that the disclosure be sufficient to teach one of skill in the art how to make and use the claimed subject matter without undue experimentation. As discussed above, the specification discloses the nucloesides/nucleotides with three different blocking groups and describes conditions for selective orthogonal deprotection thereof in detail. Based upon the disclosure those skilled in the art can generate a combinatorial library as instantly claimed.

Further, a patentee not only is entitled to narrow claims particularly

directed to a specific embodiment, but also to broad claims that define an invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). As discussed above, applicant has described the nucleosides/nucleotides with three reactive groups, exemplary blocking groups and conditions for removal thereof. Based on this disclosure, a person of skill in the art can choose various other blocking groups for protection of reactive moieties on nucleosides/nucleotides and generate the combinatorial libraries within the scope of instant claims without undue experimentation.

DECLARATION

Notwithstanding the above arguments, attached is a DECLARATION under 37 C.F.R. §1.132, of Hubert Köster to evidence that the process for generating a combinatorial library as claimed can be practiced by a skilled artisan based on the application disclosure and the information available in the art. The DECLARATION shows that using the teachings of the application, three different blocking groups removable under three different conditions can be selected to block the reactive moieties on nucleosides/nucleotides and a combinatorial library can be generated as claimed, by selectively removing the blocking groups and derivatizing the immobilized molecule at at least one reactive moiety with a unique substituent.

It is noted that the level of skill in the biotechnical arts is recognized to be high (see, *e.g.*, *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986). Further, various blocking groups for protection of reactive moieties on nucleosides/nucleotides as used in the claimed process, were known to the skilled artisan at the time of filing.

In preparing the nucleosides/nucleotides with three blocking groups removable under three different conditions disclosed in the application, Dr. Huber Köster followed the criteria for selective orthogonal deprotection set forth in the application and used standard methods as known to those of skill in the art as of the earliest priority date of the above-captioned application. Since

those of skill in this art typically have advanced degrees, Dr. Köster, who has a Ph.D. degree, is representative of a person of skill in this art with respect to performing experiments in accord with a disclosed protocol.

The DECLARATION further demonstrates that a person of skill in the art knows three different protecting groups removable under three different conditions, and based on the application disclosure, can use them for generation of combinatorial library of nucleosides/nucleotides as instantly claimed.

Rebuttal to Arguments in the Office Action

The Office Action alleges that the specification disclosure is based on the use of **3 or more protecting groups which are present on an oligonucleotide not on a single molecule** (nucleotide or nucleobase as in the claims).

Applicant respectfully submits that the instantly claimed process is mischaracterized in the Office Action. The claimed process is for generating a combinatorial library of molecules selected from a **nucleoside** and a **nucleotide** and requires presence of three reactive moieties on nucleosides/nucleotides and not nucleobase as alleged in the Office Action. As discussed above, the application discloses three protecting groups for reactive moieties on a single nucleoside/nucleotide and a skilled artisan can further choose nucleosides/nucleotides with an additional reactive -OH group that can be protected as described in the application, when ribose is present as a sugar moiety in the nucleosides/nucleotides. The reactive moieties can be deprotected as described in the application.

REJECTION OF CLAIMS 4 AND 11-16 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 4 and 11-16 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the application regard as the invention. The Office Action notes that the claims recite "plurality of immobilized molecules selected from a nucleoside or nucleotide, wherein each molecule

contains 3 to 10 reactive moieties". The Office Action alleges that it is not clear whether applicants mean that each nucleotide has 3 to 10 reactive moieties or plurality of molecules have 3 or more protecting groups. The Office Action urges that the specification examples in the schemes are drawn to the use of different protecting groups on different nulceobases.

As discussed above, amended claim 4 recites "...plurality of immobilized molecules selected from a nucleoside or nucleotide, wherein **each molecule** contains 3 reactive moieties...". Therefore, the three reactive moieties are present on each nucleoside/nucleotide. The specification, as discussed above, exemplifies nucleosides/nucleotides with 3 reactive moieties protected with three different blocking groups that can be removed under three different conditions.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Köster et al. Group Art Unit: 1639

Serial No.: 09/171,625 Examiner: Ponnalpuri, P.

Filed: July 2, 1999

For: A COMBINATORIAL PROTECTING GROUP STRATEGY FOR MULTIFUNCTIONAL MOLECULES

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, HUBERT KÖSTER, declare as follows:

1. I am a co-inventor of and familiar with the subject matter of the above-captioned application.

2. I received a Ph.D. in Chemistry from Hamburg University, Germany, and did post-graduate research work at the Max Planck Institute for Experimental Medicine in Göttingen, Germany. I was appointed Professor of Organic Chemistry and Biochemistry in 1982 at Hamburg University. I hold more than 20 patents and I have authored more than 110 publications.

3. I am a founder of several biotechnology companies, including HK Pharmaceuticals. I am Chief Executive Officer of HK Pharmaceuticals.

4. As an inventor of the above-captioned application, I have carefully reviewed the application. The application describes a process for generating a combinatorial library containing the steps of preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 reactive moieties, each reactive moiety being blocked by a blocking group, wherein the three blocking groups on each immobilized molecule are independently removable under three different conditions; and removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library. The specification

describes preparation of an exemplary nucleotides within the scope of claim 1, on pages 22 and 23 in schemes 7 and 8, respectively. As demonstrated therein, compounds **2a-d** and **1** represent molecules selected from a nucleoside and nucleotide wherein each molecule contains 3 reactive moieties each reactive moiety is blocked by a blocking group. The blocking groups on each molecule are independently removable under at least three different conditions. The blocking groups exemplified in schemes 7 and 8 include trityl group for protection of 3' OH group, npe/npeoc for base protection and β-cyanoethyl for phosphate protection. The specification describes the conditions for selective orthogonal deprotection of these blocking groups on page 9, table 1.

The specification discusses stability of various base protecting groups such as nps (specification page 13, line 22 through page 14, line 11), acetyl and benzoyl groups (specification page 13, lines 19-21); various phosphate protecting groups including, p-chlorophenyl, 2,5-dichlorophenyl, o-chlorophenyl (specification page 13, lines 7-21); protection of 3'-OH and 5'-OH groups with Fmoc (specification page 16, reaction scheme 3), dimethoxytrityl and levulinic acid ester group (specification page 9, lines 6-14 and page 15, lines 11-20). The specification, thus sets forth the criteria for selection of protecting groups and deprotection reagents under reaction conditions of claimed combinatorial libraries.

5. Furthermore, at the time of filing and before, ~~knew~~ various blocking groups were known for the protection of the reactive moieties in nucleosides/nucleotides. The specification cites several articles that disclose OH, phosphate and base protection groups and deprotection reagents as follows:

The protection of the carbohydrate 5' and/or 3'- hydroxy functions with protecting groups, including but not limited to, **trityl, acetyl, benzoylpropanoyl**; phosphate protection with **β-cyanoethyl, chlorophenyl**; and protection of the amino function on bases with **dimethylaminomethylene, acyl** is discussed in extensive details in the article published by Amarnath *et al.*, Chemical Reviews, **1977**, 77, 183-217. The protecting groups are categorized as acid labile, base

labile and groups removable under neutral conditions. The reference describes reagents and conditions for deprotection of the protecting groups, for example 2,4-dinitrobenzenesulfenyl protecting group on 5'-hydroxy site of nucleosides can be removed by thiophenol in phenol.

An extensive review published by E. Sonveaux, *Bioorg. Chem.,* **1986,** 14, 274-325, discusses several protecting groups, including but not limited to, various **acyl groups, DmTr and pixyl,** for use in different oligonucleotide synthesis methods for individual bases and for 3'- and 5'-hydroxy groups.

An article by Reese, C. B., *Tetrahedron,* **1978,** 34, 3143-79, reviews various protecting groups, including but not limited to **benzoyl, p-anisoyl** for -OH functionalities and for the bases.

Watkins *et al.* in *J Am. Chem. Soc.,* **1982,** 104, 5702-08, have described use of **benzyloxycarbonyl** group removable under neutral hydrogenolysis conditions protection of bases in nucleoside/nucleotide molecules.

Gioeli *et al.* in *J. Chem. Soc. Chem. Commun.,* **1982,** 672-74, have described **Fmoc group** removable by basic reagents such as aqueous ammonia, piperidine, ethanolamine or morpholine, in the 5'-*O*-Fmoc-2'-deoxythymidine having orthogonal deprotection properties described in the instant application.

Kharasch *et al. J. Amer. Chem. Soc.,* **1953,** 75, 2658-60, have described **2,4-dinitrophenylsulfenyl (dnps) group** in the dnps ethyl ester which reveals selective deprotection properties with deprotection reagents described in the instant application.

Further literature, describing various protecting groups for the reactive moieties on nucleosides/nucleotides, that was available before the filing of the application includes:

U.S. Patent Nos. 5,763,599 and 5,652,358, describe **phenoxyacetyl, benzoyl, isobutyroyl, p-(t-butyl)benzoyl and p-(t-butyl)phenylacetyl** protecting group for nucleotide bases.

Köster et al., Tetrahedron 37, 363-369, and Ti *et al.* J. Am. Chem. Soc. 1982, 104: 1316-1319, report several **acyl protecting groups** for use in

oligonucleotide synthesis. Comparative rates of deacylation of various acyl protecting groups in MeOH/NaOH mixture are also reported.

Rasmussen *et al.* J. Am. Chem. Soc. 1967, 89(21): 5439-45, disclose **pivaloyloxymethyl protecting group** removable under mildly basic conditions, for adenine.

Hayakawa *et al.* J. Am. Chem. Soc. 1990, 112: 1691-1696, describe **allyloxycarbonyl (AOC) protecting group** for nucleoside bases. AOC group can be removed by palladium(O) catalyzed reaction under mild conditions.

Vu *et al.* Tetrahedron Letters, 1990, 31, 7269-7272, describe **dialkylformamidine and isobutyryl** protection of nucleosides. Deprotection can be achieved under mild basic conditions.

Dreef-Tromp *et al.* Tetrahedron Letters, 1990, 31, 427-430, describe **2-(*tert*-butyldiphenylsilyloxymethyl)benzoyl protecting group** removable under neutral conditions by fluoride ion.

U.S. Patent No. 5,614,622 describe the use of **5-Pentenoyl** moiety as nucleoside amino protecting group. It can be deprotected by chemoselective removing agents for example, halogens in water or pyridine/alcohol or by nonchemoselective removing agents such as aqueous ammonium hydroxide or alcoholic ammonia.

Caruthers *et al.* Nucleosides & Nucleotides, 4(1&2), 95-105, have described various **amidine protecting groups** which can be removed under basic condition, for nucleoside bases.

Letsinger *et al.* J. Am. Chem. Soc. 1969, 91:12: 3356-59, describe **β-benzoylpropionyl and benzoylformyl** for -OH protection of nucleosides and **isobutyloxycarbonyl** for $-NH_2$ protection during oligonucleotide synthesis. These can be removed under neutral conditions.

Vinogradov *et al.* Tetrahedron Letters 1993, 34, 5899-5902, describe **isopropoxyacetal group** for the protection of the exocyclic amine of the nucleic bases. Deprotection was achieved under basic conditions.

Kamimura *et al.* Tetrahedron Letters 1983, 24, 2775-2778, reported

diphenylcarbamoyl group for protection of 6-O and **propionyl group** for protection on amino group in guanine. It was removed by ammonia + pyridine.

McBride *et al.* Tetrahedron Letters 1983, 24, 2953-56, reported **N-methyl-2-Pyrrolidine amidine** group as deoxynucleoside protecting group and removal was achieved by ethylenediamine:phenol.

Ogilvie *et al.* Tetrahedron Letters 1982, 23, 2615-18, describe **Levulinyl group** for amino protection in nucleosides and hydrazine as deprotection reagent.

Froehler *et al.* Nucleic Acid Research 1983, 11, have reported **dialkylformamidine protecting group** removable with ammonia, for N protection in deoxyadenosine.

Therefore, there is multitude of literature available that describes various protective groups used to block the reactive moieties in nucleosides/nucleotides.

6. Based on the wealth of information available in the art about protecting groups/deprotection conditions, and the conditions for selective orthogonal deprotection set forth in the application, three different protecting groups removable under three different conditions for protection of reactive moieties in a nucleoside/nucleotide could be selected and used as claimed in the instant process. For example, a representative set of protecting groups removable under selective and orthogonal conditions is: 3' and 5'-OH protection by a pixyl group (removed under acidic conditions), base protection with benzyloxycarbonyl group (removed under reductive conditions) and phosphate protection with o-chlorophenyl group (removed with $(n\text{-butyl})_4NF$).

* * *

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

HUBERT KÖSTER

Date: 10/27/03

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